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**ORIGINAL RESEARCH**

# Pathological Analysis of Liver Fibrosis: A Comparative Study of Alcoholic and Non-Alcoholic Steatohepatitis

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## ABSTRACT

**Aim:** This study aimed to compare the pathological features of liver fibrosis in patients with alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH), focusing on clinical, biochemical, and histopathological characteristics. **Material and Methods:** This observational, comparative study included 160 patients diagnosed with liver fibrosis due to ASH or NASH, with 80 patients in each group. Data were collected from electronic medical records, including demographic, clinical, and laboratory parameters. Liver biopsies were assessed histologically for fibrosis stage (METAVIR) and pathological features such as steatosis, hepatocyte ballooning, and Mallory-Denk bodies. Statistical analysis included chi-square tests and independent t-tests, with a significance level of $p < 0.05$. **Results:** NASH patients exhibited significantly higher BMI ($31.45 \pm 4.82$ kg/m² vs. $25.65 \pm 3.21$ kg/m², $p < 0.001$) and metabolic comorbidities such as diabetes (47.50% vs. 12.50%, $p < 0.001$) and dyslipidemia (62.50% vs. 15.00%, $p < 0.001$). Histologically, steatosis was more prevalent in NASH (93.75% vs. 37.50%, $p < 0.001$), while Mallory-Denk bodies were more common in ASH (68.75% vs. 37.50%, $p < 0.001$). Pericellular fibrosis and portal inflammation were significantly higher in NASH (87.50% and 75.00%) than in ASH (56.25% and 50.00%, $p < 0.001$). Fibrosis staging revealed mild fibrosis (F1) was more frequent in NASH (31.25%) than in ASH (18.75%, $p = 0.045$). **Conclusion:** ASH and NASH exhibit distinct pathological profiles despite overlapping features. ASH is characterized by Mallory-Denk bodies, while NASH shows greater pericellular fibrosis and portal inflammation. These findings underscore the need for tailored diagnostic and therapeutic strategies for ASH and NASH to mitigate disease progression effectively.

**Keywords:** Alcoholic steatohepatitis, Non-alcoholic steatohepatitis, Liver fibrosis, Histopathology, METAVIR scoring system



## INTRODUCTION

Liver fibrosis is a pivotal feature of chronic liver diseases, signifying the progressive accumulation of extracellular matrix proteins in response to sustained liver injury. Among the various etiologies of liver fibrosis, alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) represent two major conditions that share histopathological similarities yet differ significantly in their underlying causes and risk factors. Understanding these differences is crucial for the development of targeted diagnostic and therapeutic strategies.[1]ASH is primarily driven by excessive alcohol consumption, which induces hepatocellular injury through oxidative stress, mitochondrial dysfunction, and the production of inflammatory mediators. Chronic alcohol intake not only causes steatosis but also promotes fibrosis, leading to cirrhosis in advanced stages. In contrast, NASH is associated with metabolic syndrome, characterized by obesity, insulin resistance, dyslipidemia, and hypertension. This condition has become the leading cause of chronic liver disease globally, largely due to the rising prevalence of obesity and type 2 diabetes.[2] The global burden of chronic liver diseases, including ASH and NASH, continues to rise, posing a significant challenge to public health systems. ASH remains prevalent in regions with high rates of alcohol consumption, while

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NASH is rapidly becoming a leading cause of liver-related morbidity and mortality due to the obesity epidemic. The distinct yet overlapping risk factors for these conditions necessitate a deeper understanding of their progression and impact on liver pathology. Furthermore, the interplay between genetic predispositions, environmental factors, and lifestyle choices adds complexity to the pathogenesis of liver fibrosis in these diseases.[3] Advancements in diagnostic techniques, including imaging modalities and non-invasive biomarkers, have improved the ability to detect and stage liver fibrosis. However, liver biopsy remains the gold standard for assessing fibrosis and differentiating between ASH and NASH. The histological evaluation not only provides insights into the severity of fibrosis but also reveals unique pathological hallmarks associated with each condition. By comparing these features, this study aims to bridge existing knowledge gaps and enhance the clinical approach to managing ASH and NASH, ultimately improving patient outcomes through tailored treatment strategies.[4,5]Despite their differing etiologies, ASH and NASH share overlapping histological features, including steatosis, hepatocyte ballooning, and lobular inflammation. However, certain pathological characteristics, such as Mallory-Denk bodies, are more commonly observed in ASH, whereas NASH tends to show a higher prevalence of pericellular fibrosis and portal inflammation. These distinctions reflect the unique pathophysiological mechanisms underlying each condition.[6,7]The comparative analysis of liver fibrosis in ASH and NASH has significant clinical implications. Early identification of fibrosis stages is critical, as progression to cirrhosis is associated with an increased risk of liver-related complications, including hepatocellular carcinoma and liver failure. Moreover, understanding the distinct pathological features of ASH and NASH could aid in refining diagnostic criteria and improving the accuracy of non-invasive diagnostic tools.

## MATERIAL AND METHODS

This observational, comparative study was conducted to evaluate and compare the pathological features of liver fibrosis in patients with alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH). A total of 160 patients were included, with 80 patients in each group. The study included patients with confirmed liver fibrosis secondary to ASH or NASH. Patients were identified through electronic medical records and selected based on established inclusion and exclusion criteria. Each patient underwent detailed clinical, biochemical, and histopathological assessments.The study was conducted following the principles of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board (IRB), and patient confidentiality was maintained throughout the study. Due to its retrospective nature, informed consent was waived.

### Inclusion Criteria

1. Adult patients aged 18–75 years.
2. Histologically confirmed liver fibrosis due to ASH or NASH.
3. Complete clinical, laboratory, and imaging data available.

### Exclusion Criteria

1. Co-existing liver diseases (e.g., viral hepatitis, autoimmune hepatitis, or hereditary liver disorders).
2. History of hepatotoxic drug use within the past six months.
3. Insufficient or inadequate liver biopsy samples.

### Methodology

Demographic, clinical, and biochemical data were systematically collected from patient records to ensure a comprehensive evaluation. Demographic variables included age, sex, and body mass index (BMI), providing a baseline characterization of the study population. Clinical variables encompassed alcohol consumption history, including quantity and duration, along with the presence of metabolic comorbidities such as diabetes, hypertension, and dyslipidemia. Laboratory parameters were also analyzed, focusing on liver function tests, lipid profiles, and inflammatory markers to assess the biochemical status and potential contributing factors to liver fibrosis.

### Histopathological Assessment

Liver biopsies were analyzed by two experienced pathologists blinded to clinical data to ensure unbiased evaluation. Fibrosis was staged using the METAVIR scoring system (F0–F4). Additional histopathological features, including steatosis, hepatocyte ballooning, inflammation, and Mallory-Denk bodies, were recorded and compared between ASH and NASH groups.

### Comparative Analysis

The primary focus was to compare the fibrosis stage and histopathological characteristics between ASH and NASH groups. Secondary analyses evaluated correlations between fibrosis severity and clinical variables such as BMI, diabetes, and alcohol consumption levels.

### Statistical Analysis

Data were analyzed using statistical software SPSS 26.0 version. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) and compared using independent t-tests or Mann-Whitney U tests. Categorical variables were expressed as proportions and compared using chi-square tests. A p-value of $<0.05$ was considered statistically significant. Inter-rater reliability for histopathological assessments was determined using Cohen's kappa coefficient.

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## RESULTS

### Demographic Characteristics

The demographic analysis revealed significant differences between the ASH and NASH groups. The mean age of patients in the ASH group was 52.34 ± 10.52 years, slightly higher than 50.12 ± 11.20 years in the NASH group, but this difference was not statistically significant ($p = 0.234$). Gender distribution showed a stark contrast; 87.50% of ASH patients were male, compared to only 50.00% in the NASH group, highlighting a significant male predominance in ASH ($p < 0.001$). Conversely, the NASH group had an equal gender distribution with 50.00% females. Body mass index (BMI) was significantly higher in the NASH group (31.45 ± 4.82 kg/m²) compared to the ASH group (25.65 ± 3.21 kg/m², $p < 0.001$). Obesity prevalence was also markedly higher in NASH (75.00%) compared to ASH (22.50%, $p < 0.001$). Smoking history was more common in the ASH group, with 60.00% of patients reporting smoking compared to 25.00% in the NASH group ($p < 0.001$).

### Clinical Characteristics

Clinical differences were pronounced between the two groups. Alcohol consumption was specific to the ASH group, averaging 38.52 ± 12.83 units per week. Diabetes prevalence was significantly higher in NASH patients (47.50%) compared to ASH patients (12.50%, $p < 0.001$). Similarly, hypertension was more prevalent in NASH (52.50%) than in ASH (18.75%, $p < 0.001$), as was dyslipidemia (62.50% in NASH vs. 15.00% in ASH, $p < 0.001$). Fatigue, a common symptom, was reported by 68.75% of NASH patients compared to 37.50% of ASH patients ($p < 0.001$). Abdominal pain was more frequent in NASH (43.75%) than in ASH (25.00%, $p = 0.018$). The prevalence of hepatic encephalopathy and ascites was low in both groups, with no statistically significant difference between them ($p > 0.05$).

### Laboratory Parameters

Laboratory findings highlighted significant biochemical differences. ALT levels were higher in the NASH group (72.85 ± 25.64 U/L) than in the ASH group (65.42 ± 22.15 U/L, $p = 0.045$). Conversely, AST levels were significantly elevated in ASH (80.32 ± 30.23 U/L) compared to NASH (58.72 ± 20.52 U/L, $p < 0.001$). Lipid profiles showed that total cholesterol (211.54 ± 42.35 mg/dL vs. 175.25 ± 35.72 mg/dL, $p < 0.001$) and triglycerides (230.32 ± 50.41 mg/dL vs. 160.54 ± 48.23 mg/dL, $p < 0.001$) were markedly higher in NASH. Inflammatory marker CRP was significantly elevated in NASH (18.92 ± 7.23 mg/L) compared to ASH (12.34 ± 6.84 mg/L, $p < 0.001$). Platelet counts were also higher in NASH (198.42 ± 30.65 x10³/µL) than in ASH (155.60 ± 25.32 x10³/µL, $p < 0.001$). Serum albumin and bilirubin levels showed no significant differences ($p > 0.05$).

### Fibrosis Staging (METAVIR)

Fibrosis staging revealed that mild fibrosis (F1) was significantly more common in NASH (31.25%) than in ASH (18.75%, $p = 0.045$). Moderate (F2), severe fibrosis (F3), and cirrhosis (F4) showed similar distributions between the groups, with no statistically significant differences ($p > 0.05$). Fibrotic bridging was more prevalent in NASH (56.25%) compared to ASH (43.75%), but the difference did not reach statistical significance ($p = 0.065$).

### Histopathological Features

Histopathological comparison revealed stark differences. Steatosis was significantly more prevalent in NASH (93.75%) than in ASH (37.50%, $p < 0.001$). Hepatocyte ballooning was also more common in NASH (81.25%) compared to ASH (62.50%, $p = 0.008$). Conversely, Mallory-Denk bodies were more frequent in ASH (68.75%) than in NASH (37.50%, $p < 0.001$). Portal inflammation and pericellular fibrosis were significantly higher in NASH (75.00% and 87.50%, respectively) compared to ASH (50.00% and 56.25%, respectively, $p < 0.001$). Cholestasis was more commonly observed in ASH (15.00%) than in NASH (6.25%, $p = 0.034$).

**Table 1: Demographic Characteristics**

| Variable | ASH (n = 80) | NASH (n = 80) | p-value |
|---|---|---|---|
| Age (years, mean ± SD) | 52.34 ± 10.52 | 50.12 ± 11.20 | 0.234 |
| Gender | | | <0.001 |
| Male (%) | 70 (87.50%) | 40 (50.00%) | |
| Female (%) | 10 (12.50%) | 40 (50.00%) | |
| BMI (kg/m², mean ± SD) | 25.65 ± 3.21 | 31.45 ± 4.82 | <0.001 |
| Obesity (%) | 18 (22.50%) | 60 (75.00%) | <0.001 |
| Smoking history (%) | 48 (60.00%) | 20 (25.00%) | <0.001 |

**Table 2: Clinical Characteristics**

| Variable | ASH (n = 80) | NASH (n = 80) | p-value |
|---|---|---|---|
| Alcohol consumption (units/week) | 38.52 ± 12.83 | - | <0.001 |
| Diabetes (%) | 10 (12.50%) | 38 (47.50%) | <0.001 |
| Hypertension (%) | 15 (18.75%) | 42 (52.50%) | <0.001 |
| Dyslipidemia (%) | 12 (15.00%) | 50 (62.50%) | <0.001 |

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| | | | |
|---|---|---|---|
| Fatigue (%) | 30 (37.50%) | 55 (68.75%) | <0.001 |
| Abdominal pain (%) | 20 (25.00%) | 35 (43.75%) | 0.018 |
| **Hepatic encephalopathy (%)** | 8 (10.00%) | 6 (7.50%) | 0.512 |
| **Ascites (%)** | 12 (15.00%) | 10 (12.50%) | 0.634 |

**Table 3: Laboratory Parameters**

| Parameter | ASH (n = 80) | NASH (n = 80) | p-value |
|---|---|---|---|
| ALT (U/L, mean ± SD) | 65.42 ± 22.15 | 72.85 ± 25.64 | 0.045 |
| AST (U/L, mean ± SD) | 80.32 ± 30.23 | 58.72 ± 20.52 | <0.001 |
| Total cholesterol (mg/dL) | 175.25 ± 35.72 | 211.54 ± 42.35 | <0.001 |
| Triglycerides (mg/dL) | 160.54 ± 48.23 | 230.32 ± 50.41 | <0.001 |
| CRP (mg/L, mean ± SD) | 12.34 ± 6.84 | 18.92 ± 7.23 | <0.001 |
| Serum albumin (g/dL) | 3.92 ± 0.52 | 3.78 ± 0.47 | 0.124 |
| **Platelet count (x10³/µL)** | 155.60 ± 25.32 | 198.42 ± 30.65 | <0.001 |
| **Bilirubin (mg/dL)** | 1.45 ± 0.65 | 1.32 ± 0.54 | 0.098 |

**Table 4: Fibrosis Staging (METAVIR)**

| Fibrosis Stage | ASH (n = 80) | NASH (n = 80) | p-value |
|---|---|---|---|
| F0 (No fibrosis) | 5 (6.25%) | 3 (3.75%) | 0.375 |
| F1 (Mild fibrosis) | 15 (18.75%) | 25 (31.25%) | 0.045 |
| F2 (Moderate fibrosis) | 25 (31.25%) | 20 (25.00%) | 0.120 |
| F3 (Severe fibrosis) | 20 (25.00%) | 22 (27.50%) | 0.665 |
| F4 (Cirrhosis) | 15 (18.75%) | 10 (12.50%) | 0.234 |
| **Fibrotic bridging (%)** | 35 (43.75%) | 45 (56.25%) | 0.065 |

**Table 5: Histopathological Features**

| Feature | ASH (n = 80) | NASH (n = 80) | p-value |
|---|---|---|---|
| Steatosis (%) | 30 (37.50%) | 75 (93.75%) | <0.001 |
| Hepatocyte ballooning (%) | 50 (62.50%) | 65 (81.25%) | 0.008 |
| Inflammation (%) | 45 (56.25%) | 55 (68.75%) | 0.120 |
| Mallory-Denk bodies (%) | 55 (68.75%) | 30 (37.50%) | <0.001 |
| Portal inflammation (%) | 40 (50.00%) | 60 (75.00%) | 0.003 |
| **Pericellular fibrosis (%)** | 45 (56.25%) | 70 (87.50%) | <0.001 |
| **Cholestasis (%)** | 12 (15.00%) | 5 (6.25%) | 0.034 |

## DISCUSSION

The study compared the demographic, clinical, biochemical, and histopathological characteristics of patients with alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH). The mean age of ASH patients (52.34 ± 10.52 years) and NASH patients (50.12 ± 11.20 years) was comparable, with no statistically significant difference ($p = 0.234$). These findings align with data from Gao et al. (2019), who reported a mean age of 50–55 years for ASH patients and slightly younger ages for NASH patients due to the earlier onset of metabolic syndrome-related liver disease.[8]Gender distribution in ASH showed a marked male predominance (87.50%) compared to NASH (50.00%), which had equal gender representation. This pattern reflects findings from Mantena et al. (2020), who reported that ASH predominantly affects males due to higher alcohol consumption, whereas NASH affects both sexes equally, correlating with obesity and metabolic syndrome prevalence.[9]BMI was significantly higher in NASH patients (31.45 ± 4.82 kg/m²) than in ASH patients (25.65 ± 3.21 kg/m², $p < 0.001$), consistent with studies by Younossi et al. (2018), which highlighted obesity as a defining feature of NASH.[10] The prevalence of obesity in the NASH group (75.00%) compared to the ASH group (22.50%) mirrors findings by Ahmed et al. (2022), who reported obesity rates of 70–80% in NASH.[11]

The clinical features demonstrated clear distinctions. Alcohol consumption, exclusive to ASH patients (38.52 ± 12.83 units/week), is the primary driver of ASH pathology. In contrast, metabolic comorbidities were significantly higher in the NASH group, with diabetes present in 47.50% of NASH patients compared to 12.50% of ASH patients ($p < 0.001$). These findings are consistent with research by Friedman et al. (2018), which linked NASH with metabolic syndrome components, including diabetes and hypertension.[12]Hypertension (52.50% vs. 18.75%, $p < 0.001$) and dyslipidemia (62.50% vs. 15.00%, $p < 0.001$) were also significantly higher in the NASH group. Younossi et al. (2019) similarly highlighted these comorbidities as hallmarks of NASH.[13]Fatigue was reported in 68.75% of NASH patients versus 37.50% of ASH patients ($p < 0.001$), consistent with Zhang et al. (2021), who associated fatigue with the systemic inflammatory state in NASH.[14]

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Biochemical profiles reflected the differing etiologies. ALT levels were significantly higher in NASH patients (72.85 ± 25.64 U/L) than in ASH patients (65.42 ± 22.15 U/L, $p = 0.045$), whereas AST levels were elevated in ASH patients (80.32 ± 30.23 U/L) compared to NASH (58.72 ± 20.52 U/L, $p < 0.001$). This AST>ALT pattern in ASH aligns with findings by Crabb et al. (2018), which attributed this to mitochondrial damage caused by alcohol.[15]Lipid abnormalities were more pronounced in NASH, with total cholesterol (211.54 ± 42.35 mg/dL vs. 175.25 ± 35.72 mg/dL, $p < 0.001$) and triglycerides (230.32 ± 50.41 mg/dL vs. 160.54 ± 48.23 mg/dL, $p < 0.001$) significantly elevated. These findings are consistent with Kumar et al. (2020), who identified dyslipidemia as a major contributor to NASH progression.[16]

Fibrosis staging showed that mild fibrosis (F1) was more common in NASH patients (31.25%) than in ASH patients (18.75%, $p = 0.045$). However, advanced fibrosis (F3/F4) and cirrhosis showed similar distributions between the groups. These results align with Chalasani et al. (2021), who found that both ASH and NASH can progress to severe fibrosis, although NASH patients often present earlier due to metabolic syndrome screening.[17]Histopathological features revealed stark differences. Steatosis was significantly more prevalent in NASH patients (93.75%) than in ASH patients (37.50%, $p < 0.001$). These findings are consistent with Bugianesi et al. (2017), who identified steatosis as a hallmark of NASH. Hepatocyte ballooning was also more frequent in NASH (81.25%) compared to ASH (62.50%, $p = 0.008$).[18]Conversely, Mallory-Denk bodies were significantly more common in ASH (68.75%) than in NASH (37.50%, $p < 0.001$), reflecting findings by Tsuchida et al. (2020), who linked these features to alcohol-induced cytoskeletal damage.[19] Portal inflammation and pericellular fibrosis were significantly higher in NASH (75.00% and 87.50%) compared to ASH (50.00% and 56.25%, $p < 0.001$), consistent with Rinella et al. (2019).[20]

## CONCLUSION

This study highlights the distinct pathological and clinical characteristics of liver fibrosis in alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH). While both conditions share overlapping histological features, such as steatosis and inflammation, ASH is more associated with Mallory-Denk bodies, and NASH demonstrates a higher prevalence of pericellular fibrosis and portal inflammation. These differences reflect unique underlying mechanisms driven by alcohol consumption in ASH and metabolic syndrome in NASH. Recognizing these distinctions is crucial for accurate diagnosis, early intervention, and the development of tailored therapeutic strategies to mitigate disease progression and associated complications.

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